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[Reprint from *The St. Louis Medical and Surgical Journal*, July, 1893.]

Inflammation and Chemotaxis.*

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Gentlemen:—When I received the valued invitation from your president to appear before you as your guest, I was not long in doubt over a subject for my remarks. For I have been occupied for two years with the application to the manifestations of disease in the skin of a doctrine, the author of which you reckon with pride among your number, and to whom personally I have to-day the honor of offering some of my results. I refer to Prof. Leber, who in his work on inflammation of the eye founded the doctrine of the rôle of chemotaxis in inflammation.

If the task of characterizing and systematizing different inflammations of other organs presents sufficient difficulty, it is infinitely more complicated when concerned with those skin diseases recognized as inflammations. This is simply from the reason that we see incomparably more inflammatory conditions in the skin, and can more readily observe their course and results, than in any of the internal organs. The number interferes with each systematic classification, and previously obtaining theories of inflammation prove insufficient. It is in this connection that it is first noticed what in inflammations of the internal organs, coming to us piecemeal and fragmentarily, is frequently overlooked—that scarcely a single disease revolves in the same circuit as another—that each is a pathological mist.

But the human mind does not like to accept oneness, and we are thus forced into generalizing, and the general and extraordi-

*Read before the Medical Section of the Heidelberg Society for Medical and Natural Science. January 29, 1893.

narily comprehensive idea of inflammation will hardly be banished from pathology. Each one must content himself with it.

How beautiful it was when Virchow's former conceptions were verified—that the living elements of the skin fell into activity and produced the symptoms of inflammation!

How satisfying again when Cohnheim, correctly in most instances, had placed injury of the blood vessels, that great riddle of pathology, in the centre of the inflammatory act.

But the study of inflammation teaches us unfailingly that certain changes characteristic of inflammation frequently happen, and just as frequently fail to take place in conditions which the clinician dare not exclude from inflammation in the skin.

In the search after and desire for a more general and comprehensive pathological principle, which should in a measure share in the clinically protean nature of inflammation, and approximate in its capacity for extension, I happened after a time upon the investigations of Pfeffer (1) and Leber (2) of the chemotactic action of certain substances upon bacteria and leucocytes. How the scales fell from my eyes! Here we have a new general principle of prime, and until now unknown, efficiency which at least for those skin inflammations known to me does all that one can expect of a general explanatory principle.

How mysteriously the chemical attraction of living material catches the fancy?

It is founded on fact, and gives, it seems to me, the foundation to the understanding of each inflammation.

This conception is not, however, entirely new; for were not the old, obscure, long-abandoned theories of inflammation also theories of attraction?

A year ago I showed in the example of Bockhardt's impetigo (1) —pure and simple epidermal abscesses developed by the yellow and white staphylococci—that diseases of the epidermis need no further explanation than the chemotactic action of staphylococci upon leucocytes; in short, their *leucotactic* action.

In this location the conditions for determining the origin of abscesses lie as favorably as in the cornea, perhaps even more so. The staphylococci are present in a non-vascular membrane—the epidermis, immediately under the horny layer, but without their proliferation, doing direct, perceptible injury to the epidermal cells.

We can, therefore, safely say that all morbid products which collect around the penetrating organisms were drawn from a distance, and drawn by these organisms alone, because no pathological changes of the prickle layer for the emigration and attraction of leucocytes come into consideration; and if we go still further we see that also in the region from which the leucocytes come—the papillary layer richly supplied with blood-vessels—there is *no perceptible injury to the blood-vessels*, or at most only a slight dilatation, and that the emigration to and around the papillary vessels after the formation of an abscess does not persist, but immediately ceases. So we are forced to the conclusion that, with the attraction of leucocytes from the papillary vessels, the entire morbid, the whole "inflammatory" process is ended.

Therefore, even though a purulent inflammation with frank abscess formation be present the entire inflammatory event resolves itself into the simple proposition of chemotactic action. This it is that stands in the centre of the phenomenon. All that we perceive further, the formation of abscesses, their encapsulation or rupture internally or externally, are but further consequences of the same cause.

All previously advanced theories are not only unnecessary, but are even insufficient for explanation, because each histological basis (cell proliferation, injury of vessels, of epithelium, of connective tissue) is absent.

This simple example of a high grade of inflammation which begins and ends with a simple chemotactic attraction of an exudate is extraordinarily instructive.

You see therefore, gentlemen, that the model is not Cohnheim's experiment upon the frog's mesentery, but is the tube of Leber in the anterior chamber of the eye filled with leucocytes, as if transformed into an abscess because it contains an active leucotactic substance.

Not the dilated blood-vessel with leucocytes upon its walls forms the centre, with the other appearances grouped around it in a circle, and the far-removed abscess being the single phenomenon at the periphery; but on the contrary, the forceful injury, the accumulation of staphylococci, represent the centre with all the capillaries at the circumference participating in the formation of the abscess in the centre, the leucocytes are not forced out from the *injured* vessels, coming by chance into the domain

of the enemy there to be fixed, but they are energetically drawn from the *uninjured vessels* after one plan, to one point. This accounts then for the rapid formation of a large drop of pus without important changes of the periphery being visible.

You will perhaps say that I substitute a new obscurity for an old one, for it would remain the same whether the leucocytes creep in, are forced in, or are allured.

This inversion of the notion of mechanical force seems to you perhaps trivial and irrelevant. But I hope to show you that this inversion of our views at one stroke explains many obscurities in the study of inflammation, and creates explanations of what was hitherto inexplicable.

Let us now turn to vesicular affections of the skin, because, for obvious reasons, these exudative inflammations of the epidermis furnish transparent examples of the chemotactic origin of inflammation. There are in the details many differences, particularly in the morphological and chemical nature of the exudates, and it is to these that I especially desire to draw your attention this evening.

An affection in recent times associated and confounded with staphylogenous impetigo is the vesicular form of eczema. One has here definitely to decide between two different vesicular forms—the ordinary vesicles of chronic eczema, and a very infrequently observed vesicular efflorescence of acute course which spontaneously or by intentional inoculation develops the organisms of eczema under the horny layer. The latter characteristic alone corresponds fully to staphylogenous impetigo in its mode of origin and structure, and it is this that we shall consider.

What the staphylococci are to the pustule in this form of eczematous vesicle are the morococci of eczema. We can hence understand why these acute vesicles are relatively infrequent, for in contradiction to staphylococci which are faculatively anaërobic, the morococci cannot well exist without oxygen. They are exquisite aërobic examples, and are consequently limited to the superficies of the skin. For if under peculiarly favorable circumstances they penetrate into the deeper layers, they very promptly die, and the affection caused by them heals rapidly and spontaneously.

I demonstrate here two preparations of the vesicles caused by morococci upon the human skin—one spontaneous, the other from inoculation.

Their similarity to impetigo consists merely in the circumstance, that in both instances the micro-organism has penetrated under the horny layer, and has attracted to itself a drop of pus, which has raised up the horny layer from the compressed prickle layer. But more important for us than this analogy are the differences between the two vesicular forms.

In the first place, the staphylococci form the well-known grape-like clusters, which are principally situated upon the summit of the drop of pus, between it and the horny layer, and later on extend in a radiate manner into the compact collection of pus without penetrating into the pus cell itself. The morococci, on the contrary, form diplococci and mulberry masses and distribute themselves regularly through the looser, more fluid pus, and become carried off by the leucocytes—clearly a result of their feeble viability after the exclusion of oxygen. The contents and structure of this vesicle, as well as the organism, present marked differences. Besides many leucocytes it contains a large amount of serum, so that the contained pus is thin and fluid; the roof, sides and floor of the vesicle are less firm and less sharply defined from the contained pus. From the roof, softened horny cells become loosened, and from the floor swollen cells form the granular and prickle layers and mix with the pus. The lymph spaces of the epidermis in the neighborhood of the vesicle are distended. There is some œdema around the vesicle. Even after the vesicle has dried down into a crust one recognizes its eczematous nature by the presence of the large amount of coagulated serum. The appearances in the papillary bodies are also unimportant in the eczematous vesicle; only in the beginning there is a broad hyperæmic areola.

In this example, though the exudate is likewise the result of chemotactic, remote action, there are important morphological and chemical differences in the exudate which indicate that *not only leucocytes* become attracted, but also a *large amount of serum*. One would judge *a priori* that an emigration of *leucocytes* without an admixture of serum to be inconceivable, and after the Cohnheim idea of the greater porosity of the vessels in inflammation it would be inconceivable. But the instance of staphylogenous impetigo and its differences from morogenous eczema teaches us better. The serum of vesicles is not a necessary concomitant of leucocytes. It comes independently into

the vesicles, and if we accept chemotaxis for leucocytes on good grounds it is inconsistent to entertain another idea of the transudation of serum, simply because serum is an amorphous albuminous body.

Now let us consider before we proceed to further conclusions certain other vesicular affections. The third preparation is from an infant of one and a half years. The eruption was vesicular and presented a certain external similarity to the vesicles of vaccinia. The vesicles occupied chiefly the upper part of the face and extended to the hairy scalp, cheek and chin. Some vesicles also appeared in the inguinal region. The baby was afterward vaccinated and with success.

Here you have again a vesicle constructed entirely after the type of impetigo. The horny layer is raised up from the prickle layer by an exudate the size of a lentil, and we find the cause of this at once on the apex of the exudate on the underside of the horny layer—a colony of cocci penetrated through a sweat pore*, and differing in many particulars from the accumulations of both staphylococci and morococci. One cannot, however, definitely characterize from one case alone.

The epidermis and the papillary bodies appear entirely normal and only mechanically compressed. But what is particularly interesting to us is, that the exudate consists of pure serum. Not one white blood corpuscle is in the vesicle or at its base. Now it is, according to the present idea, entirely possible that in inflammation serum *relatively* free from leucocytes leaves the capillaries; but when it is *entirely* free from leucocytes the conviction becomes necessary that the few leucocytes that leave the blood-vessel normally are prevented from emigration, and that consequently the leucocytes are actually repelled.

This third example teaches us further that the mixing of serum and leucocytes in the vesicle of eczema is not given *eo ipso* by a certain grade of inflammation. We have, then, before us, a pure serum vesicle, as impetigo was a pure pustule. We are the more forced to the belief that each inflammation—causing organisms after its own peculiar properties—attracts a definite formed or unformed constituent of the blood and repels others, and in this manner creates a certain kind of exudate. It be-

*A rare occurrence. The sweat pores generally enjoy an immunity from bacterial invasion.

comes ever clearer that between the cause of inflammation and the exudate there exists a constant and real relation, but not such as we were hitherto accustomed to accept between the exudation and a certain degree of vascular or tissue injury.

I could cite you, gentlemen, solely from the instance of vesicular affections, a great many more examples, amply proving each in the same manner as above; but I shall content myself with giving only one more, which shows that the chemotactic selection of unformed blood constituents is in each case clearly and accurately defined.

In the case of the ten year old child H., there has appeared, for four years, upon the buttocks and extensor surfaces of the thighs, at greatly varying intervals, round or irregularly shaped, fairly large vesicles, from the size of a pea to that of a lentil. At present small yellow pustules with reddened bases appear in crops. From its clinical aspect one could suppose an impetigo of peculiar course and extent, but the histological examination reveals something quite new. The entire efflorescence in all its parts is beset with stringy fibrin, not only the swollen horny roof of the vesicle, but also the vesicular contents and the entire prickle layer underneath. In the interior of the vesicle the contained leucocytes as well as the epithelium of the vesicular floor are entangled in a dense network of fibrin. A large number of leucocytes have pushed through the cutis under the vesicle, which appears hyperæmic and œdematous.

As for the organisms causing this bullous skin inflammation, we find in the central section only one definite kind—small grape cocci, which, without being anywhere enclosed in leucocytes, stud the vesicular contents in its midst; further than this we meet with no micro-organisms.

That we are not concerned here with the ordinary grape cocci is shown by the differences in size and form, upon which I shall not now enter, and by the striking amount of fibrin which is conspicuously absent in common staphylococcous suppuration.

It is not admissible here to speak of a mere variation in the usual process of inflammation—a simple surplus of fibrin—as if fibrin must be or could always be present at certain stages. But here the fibrin is present in quantity so disproportionate that we do not find a similarly great amount even in the typical fibrinous inflammation—erysipelas—and further, the fibrin appears at the

very height of the process of formation of the vesicle. It does not in all probability originate at the decline of the efflorescence from degenerated leucocytes and washed-out epithelium, for all the cellular constituents are in good condition, easily stained, as are also the protoplasm and nuclei; and besides they are all entangled in the compact mass of fibrin which fills all the lymph spaces of the epithelium. So no other alternative is left us but to confess that, besides many leucocytes, here we have a nearly exclusively fibrinous substance which occupies the position of ordinary serum from the blood-vessels, and has followed the chemotactic attraction of micro-organisms.

Now let us review in mind the four vesicles: We have in the impetigo pustule a pure leucotactic, in the vesicle of eczema a leuco-serotactic, in the third vesicle a pure serotactic, and in the fourth a leuco-fibrinotactic action of the micro-organisms, which represent just so many inflammations of the epidermis.

In each case we recognize the same pathogenesis: a micro-organism penetrating under the horny layer, multiplying itself in contact with the tissue juices, thereby producing toxic principles, and each after its chemical nature influencing the tissue in a larger or smaller semi-circle, and acting upon the movable elements, *i. e.*, the constituents of the lymph and blood, as well as putting the wandering cells in motion, in the widest meaning of the term.

The casting off of some tissue constituent escapes our notice, as there occurs a broadcast scattering and centrifugal dispersion; but, on the other hand, the attraction of definite formed or unformed movable elements appear very soon, for by a centrifugal confluence they form and indicate the centre of attraction. This accumulation we call an exudate; the whole process, inflammatory.

You may think, gentlemen, that the process is not exhibited as clearly upon the other parts of the skin as in vesicular affections of the epidermis. The visible punctate apertures of entrance and the unilateral direction of the poison, on the one hand, and the non-vascularity of the epidermis on the other, offer as transparent and easy objects of study as one could imagine. But I assure you that, though the appearances are so clearly presented here, the principle does not fail in other inflammations of the skin and may perhaps be equally applicable to inflammations of other organs. At all events, it facilitates the analogies of the phenomena in a very welcome manner.

Let me mention only one point which is extremely valuable in the explanation of many dermatoses: the principle of chematoxis always involves the idea of remote action of micro-organisms. This is moreover dependent upon certain external conditions. The micro-organisms must multiply themselves and can accumulate up to a certain point in order to form their toxine, and their surroundings must to a certain extent be moistened to allow a diffusion of these toxines. I do not believe, for example, that the great mulberry masses of morococci, such as we so often find in dry horny scales, can attract an exudate in the form of a vesicle; but I do believe that a new proliferation of cocci and a moistening of the epidermis are necessary conditions for it. But if the necessary conditions are fulfilled we can well conceive how *the bacteria limited to the epidermis* (*horny layer*) *can influence the cutis*—a view which was to me formerly incredible, as I freely confess. It did, however, convey the possibility of an ætiological understanding of many skin inflammations, particularly catarrh of the skin and folliculitis.

In the future we may not limit with certainty the situation of the cause of inflammation in the *cutis*, because we perceive in an affection the first inflammatory changes in the cutis elements, *e. g.*, lichen planus; but we must also consider the possibility of its location in the *epidermis*—that is the possibility of remote action; not only is the principle of chemotaxis applicable to explaining and advancing the special study of skin inflammations, but it will also prove of great utility in general pathology.

That suppuration under the influence of a bacterial toxine withdraws from the isolation into which it has fallen in recent times, as distinguished from other forms of inflammation by its special etiology, is to be hailed with joy. For the notion of the apparent harmony in other inflammations, serous, fibrinous, croupous, hæmorrhagic, etc., because they can be produced in all possible cases in the same way by corresponding graduation of stimuli, will, I believe, in the future be abandoned.

The more exact the methods of study we employ, the more clearly appears to us the existence of a special *selection* in exudation. A definite chemical stimulus, even the meanest, represents an exudate of definite chemical construction, and it changes at once if the stimulus (*toxine*) changes—as for instance, if the organism die or there occur decomposition of the nutrient soil.

How mechanical stimuli to inflammation act—how few there are—how other physical causes (heating, freezing), if indeed they be not previously converted into chemical, are to be dealt with, are questions for the future. Furthermore, the diapedesis of red blood corpuscles, the class of hæmorrhagic dermatoses, the migration of fats and pigment, are to be examined from this new point of view.

Finally, let me point out the solution of two old riddles which the principle of chematoxis yields. I refer to the paradoxes which Cohnheim's studies on inflammation have left behind. 1. *The primary injury of blood-vessels*, which is to explain the extravasation of leucocytes; and (2) *the slowing of the blood current* in spite of dilatation of the blood vessels in inflammation. Now, as concerns the solution of the injury of blood-vessels, which since Cohnheim has been so zealously sought after, history has spoken. No one knew how to establish this as a constant and primary symptom, and when Cohnheim, foreseeing the negative result of these inquiries, transferred once and for all the injury from the visible cells to the invisible molecule of the vessel wall, he withdrew from general discussion his hypothesis of vascular injury. But in reality, Cohnheim would have been much pleased by the statement that there was a visible permanent injury. This cannot be discovered in the skin disease which I here exhibit.

But the principle of chematoxis makes the supposition of a primary injury to blood-vessels entirely superfluous and the research after it vain. The substances attracted from the blood-vessels and cells push their way through the *uninjured* walls, and can occasion at the most only a secondary injury to the blood-vessels in the event of the process lasting sometime. We have only to explain those sources of attraction, external to the blood-vessels, to reduce the entire phenomena to reason. We know that another attraction, namely, negative air pressure, as in the cupping glass, can draw away all the constituents of the blood from the sound vessels. And just so easy of explanation as the foregoing is the paradox of the slowing of the blood current in dilated vessels, whereby inflammatory hyperæmia is chiefly distinguished from congestive or paralytic hyperæmia.

How many ingenious explanations have been invented to clear up this fact! The example of negative external pressure in

cupping: a force of the same direction and same effect as the positive external force of chemotaxis manifestly explains this phenomenon also. While single constituents of the fluid portion of the blood are drawn out, the blood of course of the whole region must be "fixed" by the same force of attraction; and in fact the damming up of the blood and the consequent engorgement hyperæmia, as well as the fluid constituents of the blood, are under chemotactic influence.

Regularly after the kind and strength of the chemotactic force will the mural position (Randstelling) of leucocytes at one time appear; at another time great dilation of the blood-vessels with intense serotaxes, globulinotaxis and fibrinotaxis; and it is this multiplicity of conditions that we actually find in microscopical examinations of inflammatory tissue.

Viewed in this light, inflammatory hyperæmia stands far removed from the nervous or paralytic, and contains many more analogies to engorgement hyperænia, which comes from a definite physical cause, namely, elevation of atmospheric pressure and gravity. These distinguish themselves fundamentally, however, from inflammatory hyperæmia by the absence of that chemical selection of an exudate. The analogy obtains only in the rude mechanism of the process. We have here, when we think of it, a fine differential definition between the notions exudate and transudate—an exudate is hereafter the result of a chemotactic action; a transudate of a physically caused transposition of the constituents of the fluid blood from the blood channel to the tissues.

Our definition of inflammation in general would be provisionally —a tissue injury (progressive or retrogressive, exudative, proliferative, or merely nutritive) occasioned by the issue of an exudate from the blood-vessels as a result of the presence of a chemotactically active body in the tissue.

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